Complete Summary

GUIDELINE TITLE

2007 UK national guideline on the management of non-gonococcal urethritis.

BIBLIOGRAPHIC SOURCE(S)

Clinical Effectiveness Group. 2007 UK national guideline on the management of non-gonococcal urethritis. London (UK): British Association for Sexual Health and HIV (BASHH); 2008 Dec. 26 p. [84 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previously released version: Clinical Effectiveness Group. 2007 national guideline on the management of non-gonococcal urethritis. London (UK): British Association for Sexual Health and HIV (BASHH); 2007. 19 p. [83 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Non-gonococcal urethritis (NGU):

- Acute non-gonococcal urethritis
- Persistent/recurrent non-gonococcal urethritis

GUIDELINE CATEGORY

Diagnosis
Management
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To present a national guideline for the management of non-gonococcal urethritis (NGU), including recommendations on the diagnostic tests, treatment regimens, and health promotion principles needed for the effective management of NGU

TARGET POPULATION

People aged 16 years or older in the United Kingdom with non-gonococcal urethritis (NGU)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Gram stained urethral smear
2. Gram stained preparation from a centrifuged sample of a first pass urine (FPU) specimen
3. Testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

Treatment/Management

1. Patient education
2. Azithromycin
3. Doxycycline
4. Erythromycin or ofloxacin
5. Combination therapy of either azithromycin or erythromycin plus metronidazole for persistent or recurrent non-gonococcal urethritis (NGU)
6. Moxifloxacin for persistent or recurrent NGU
7. Partner(s) assessment and treatment
8. Follow up

MAJOR OUTCOMES CONSIDERED

- Sensitivity, specificity, and reliability of diagnostic tests

- Microbiological cure rate

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE searches for 1970 to present using MeSH headings "urethritis" including all documents and subheadings. Additional searches were conducted using MeSH headings "Non-gonococcal urethritis", "nongonococcal urethritis", " non-specific urethritis", "NGU", "NSU", "Chlamydia trachomatis" "Mycoplasma genitalium". The Cochrane library for 1970 to the present using keywords "Non-gonococcal urethritis", "nongonococcal urethritis", "non-specific urethritis", "NGU", "NSU". Hand search conference proceedings – BASHH (MSSVD), ISSTDR.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The original guideline document was reviewed by the Bacterial Special Interest Group and the Clinical Effectiveness Group of the British Association of Sexual Health and HIV (BASHH), and their comments incorporated. It was subsequently circulated for comments by the BASHH membership for three months.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (I-IV) and grades of recommendation (A-C) are defined at the end of the "Major Recommendations" field.

Diagnosis

The diagnosis of urethritis must be confirmed by demonstrating polymorphonuclear leucocytes (PMNLs) in the anterior urethra. This can be by means of:

i. A Gram stained urethral smear containing $\geq$5 PMNLs per high power (x 1000) microscopic field (averaged over five fields with greatest concentration of PMNLs)

and/or

ii. A Gram stained preparation from a centrifuged sample of a first pass urine (FPU) specimen, containing $\geq$10 PMNLs per high power (x 1000) microscopic field (averaged over five fields with greatest concentration of PMNLs)

- Either test can be used: both tests will identify cases missed by the other test.
- The quality of the smear is heavily dependent on how the smear is taken, and there is both inter- and intra-observer variation.
- Either a 5 mm plastic loop or cotton-tipped swab can be used and should be introduced about 1 cm into the urethra. There are no published data comparing the two, but the former is probably less traumatic to the patient (**Level of Evidence IV**).
- Positive leucocyte esterase activity on dipstick on FPU specimen correlates with non-gonococcal urethritis (NGU), and the detection of chlamydia and is considered diagnostic by some authorities. However, it does not have adequate sensitivity to be considered a reliable rapid diagnostic test for acute

NGU. Moreover, its positive predictive value for *Chlamydia trachomatis (C. trachomatis)* in asymptomatic patients is poor.

- There is controversy as to the need to perform microscopy in asymptomatic patients. Treatment will be delayed in up to 30% of those infected with *C. trachomatis* who are asymptomatic. Also a single nucleic acid amplification test (NAAT) may miss up to 3% of men with urethral chlamydia and will miss 5% to 6% of asymptomatic men infected with *Mycoplasma genitalium (M. genitalium)*. It is, however, unclear if microscopy would identify a substantial proportion of these patients, nor is *M. genitalium* currently proven to cause serious pathology (such as pelvic inflammatory disease). On the other hand, omitting microscopy in asymptomatic men will prevent diagnosing 77% to 87% of men as having a sexually transmitted infection in whom neither of the above organisms will be isolated. Indeed, relying on microscopy alone will miss up to 37% of *C. trachomatis* and up to 23% of *M. genitalium* urethral infections. There is, therefore, little justification in performing urethral microscopy in asymptomatic men (**Level of Evidence IIb**). It does, of course, remain an important test in symptomatic men for the diagnosis of gonococcal urethritis.
- While a leucocyte esterase test (1+ = positive) has variable sensitivity in diagnosing urethritis, it has a high negative predictive value (>96 to 98%), similar to that of a urethral smear, in asymptomatic men for the detection of *Neisseria gonorrhoeae (N. gonorrhoeae)* and *C. trachomatis* and thus probably *M. genitalium*. However, its positive predictive value for chlamydia in asymptomatic men is low (5.1% to 23.3%). It therefore has little place in routine practice though its good negative predictive value may be useful in population screening for *C. trachomatis*.
- Physical examination of asymptomatic men does not result in an increased diagnosis of urethral pathogens.
- The sensitivity of the smear test, but probably not the FPU is affected by the period since last passing urine. The optimum time to ensure a definite diagnosis in a symptomatic man is not known. Two to four hours is conventional.
- Symptomatic patients, in whom no discharge or urethritis is detected, could either be retested having held their urine overnight, (**Level of Evidence IV**) or given empirical treatment (**Level of Evidence IV**). With the latter choice empirical treatment to the partner(s) would be indicated.

Investigations

- All patients attending should have a test for *N. gonorrhoeae*. If a NAAT is used for *N. gonorrhoeae* a positive test should be confirmed by culture (see the National Guideline Clearinghouse [NGC] summary of the British Association for Sexual Health and HIV [BASHH] national guideline on the diagnosis and treatment of gonorrhea in adults 2005.
- *C. trachomatis* should also be sought (see NGC summary of the BASHH 2006 UK national guideline for the management of genital tract infection with *Chlamydia trachomatis*). It should be noted that even a NAAT will miss between 3% and 10% of infections.
- Commercial testing for *M. genitalium* is not available, and the place of such tests in routine clinical practice, once they become available, needs to be determined.

- A midstream urine (MSU) should be taken if a urinary tract infection is suspected. Such as, for example, if the patient complains of severe dysuria, haematuria (microscopic or macroscopic), nocturia, urinary frequency, urgency, or has not been sexually exposed. In one study, using a dipstick incorporating nitrite and leucocyte esterase tests had a sensitivity and specificity for urinary tract infection of 83% and 90% respectively.
- The traditional two-glass test adds little to the diagnosis and should be abandoned (**Level of Evidence IV**).

Management

General Advice

The following should be discussed and clear written information provided:

- An explanation of the causes of NGU, including non-infective causes, and possible short term and long term implications for the health of the patient and his partner
- The side effects of treatment and the importance of complying fully with it
- The importance of sex partner(s) being evaluated and treated
- Advice to abstain from sexual intercourse, or if that is not acceptable, the consistent use of condoms, until he has completed therapy and his partner(s) have been treated (**Level of Evidence IV**)
- Advice on safer sex
- The importance of complying with any follow-up arrangements made

Treatment

Treatment should be initiated as soon as the diagnosis is made and without waiting for the results of tests for chlamydia and cultures for *N. gonorrhoeae*. Ideally, treatment should be effective (microbiological cure rate for *C. trachomatis* >95%), easy to take (not more than twice daily), with a low side-effect profile, and cause minimal interference with daily lifestyle. However assessing treatment efficacy is problematic, as no pathogen is identifiable in over 60% of cases, and the inflammatory process may not reflect persistent infection. It is important to note that the inflammatory exudate may persist for an unknown length of time even when the putative organism has been eliminated.

Tetracyclines are generally effective against *C. trachomatis* though sporadic reports of treatment failure have been reported. While in general treatments that are effective against *C. trachomatis* appear to be also effective in NGU, tetracyclines in the doses used do not consistently eradicate *M. genitalium*, and this may also be the case with azithromycin 1 g stat (see below).

Recommended Regimens (**Grade of Recommendation A**)

- Azithromycin 1 g orally in a single dose (**Level of Evidence Ib**)

  or

- Doxycycline 100 mg twice a day for 7 days (**Level of Evidence Ib**)

Alternative Regimens (**Grade of Recommendation A**)

- Erythromycin 500 mg twice daily for 14 days (**Level of Evidence Ib**)

  or

- Ofloxacin 200 mg twice a day or 400 mg once a day for 7 days (**Level of Evidence Ib**)

Compliance with Therapy

Single dose therapy has the advantage of improved compliance, although azithromycin has not been shown to be more effective in clinical studies than doxycycline.

Sexual Contacts/Partners

All sexual partners at risk should be assessed and offered epidemiological treatment, maintaining patient confidentiality. The duration of "look back" is arbitrary; 4 weeks is suggested for symptomatic men (**Level of Evidence IIb**).

- If *C. trachomatis* or *N. gonorrhoeae* are detected, it is important to ensure that all sexual partner(s) potentially at risk have been notified (see relevant BASHH guidelines).
- Details of all contacts should be obtained at the first visit. Consent should also be obtained so that if *C. trachomatis* or *N. gonorrhoeae* are detected subsequently and the index patient does not reattend, he can be contacted and/or provider referral can be initiated for sexual contacts (**Level of Evidence IV**).
- Female contacts of men with chlamydial urethritis should be treated regardless of the results of tests for chlamydia (**Level of Evidence Ib**).

There is no direct evidence of treatment benefit to partners of men with chlamydia-negative NGU. There are, however, a number of issues which may influence decision making.

a. NGU cohort studies have looked at the effect on response of urethritis and have produced conflicting conclusions.
b. There are reports of patients with persistent or recurrent urethritis being cured only after their sexual partner received appropriate treatment.
c. Even newer NAATs may miss 3% to 10% of chlamydia-positive individuals.
d. There is also discordance in the isolation of chlamydia between partners.
e. *C. trachomatis* can clear without treatment from the cervices of women, though much less frequently from the urethras of men.
f. Finally, *M. genitalium* accounts for approximately 20% of cases and probably causes disease in women.

In the absence of randomised prospective studies, it would be prudent to treat partners of microorganism-negative NGU concurrently to potentially reduce female morbidity (**Level of Evidence IV**).

Follow Up for Patients with NGU

Follow up is important in order to assess compliance with therapy - particularly in chlamydia-positive patients. The follow up interview can be performed by phone. Patients who remain symptomatic, who have not completed their medication or who have had unprotected sexual intercourse with an untreated partner should be asked to return to the clinic and re-treated with appropriate contact tracing. (**Level of Recommendation IV**)

Persistent/Recurrent NGU

This is empirically defined as persistent or recurrent symptomatic urethritis occurring 30 to 90 days following treatment of acute NGU and occurs in 10% to 20% of patients. There is no consensus of opinion for either the diagnosis or the management of this condition. Its aetiology is probably multifactorial. *M. genitalium* may be implicated in 20% to 40%. Tetracyclines, two weeks of erythromycin or a single dose of azithromycin do not reliably eradicate this organism. In a randomised study of 398 men azithromycin 1 g resulted in failure in 16% and doxycycline 100 mg twice a day (bd) for seven days in 64% of those who returned for follow-up. In an open Scandinavian study azithromycin 500 mg stat followed by 250 mg daily for the next 4 days cured all of 19 patients. A role for *Ureaplasma urealyticum* in chronic NGU has also been suggested. Although this organism may also exhibit tetracycline resistance the therapeutic implications remain unclear. Any treatment of chronic NGU should cover *M. genitalium* and *Trichomonas vaginalis* which are not covered by standard therapy (**Level of Evidence IV**).

The only randomised controlled trial for chronic NGU showed that erythromycin for three weeks is better than placebo but did not test for *M. genitalium*, nor include partners. As there is no evidence that female partners of men with persistent/recurrent NGU are at increased risk of pelvic inflammatory disease, they do not need to be retreated if treated appropriately at first. However, in view of the emerging evidence that both doxycycline and azithromycin can fail to eradicate *M. genitalium* in men, it is likely that this is also the case in women and therefore an area where further research is needed.

Diagnosis of Persistent/Recurrent NGU

- Avoiding routine test of cure in NGU will avoid creating a "patient" in an otherwise asymptomatic individual.

Management of Persistent/Recurrent NGU

- Ensure that the patient has completed the initial course of therapy and that reinfection is not a possible cause.
- Only treat if patient has definite symptoms of urethritis, or physical signs on examination. Reassure asymptomatic patients that no further test or treatment is necessary.

Recommended Regimens (**Grade of Recommendation C**)

Patient Symptomatic or an Observable Discharge Present

1st Line

- Azithromycin 500 mg stat then 250 mg for the next 4 days (**Level of Evidence IIIb**) plus Metronidazole 400 mg twice daily for 5 days (**Level of Evidence IV**)

  or

- Erythromycin 500 mg four times daily for 3 weeks (**Level of Evidence Ib**) plus Metronidazole 400 mg twice daily for 5 days (**Level of Evidence IV**)

2nd Line

- Moxifloxacin 400 mg orally once daily for 10 days (**Level of Evidence IIb**) plus Metronidazole 400 mg twice daily for 5 days (**Level of Evidence IV**)

Note: In persistent/recurrent cases, Moxifloxacin is no longer recommended as a 1st line therapy due to recent safety concerns (an increased risk of life threatening liver reactions and other serious risks) from the UK Medicines and Healthcare Products Regulatory Agency. It is now placed as a 2nd line therapy.

Continuing Symptoms

There is only limited evidence on how best to manage patients who either remain symptomatic following a second course of treatment or who have frequent recurrences after treatment.

- Urological investigation is usually normal unless the patient has urinary flow problems and is not recommended.
- Chronic abacterial prostatitis (see BASHH guideline on prostatitis) and psychosexual causes should be considered in the differential diagnosis.
- For men with persistent or recurrent urethritis, there is currently no evidence that retreatment of an appropriately treated sexual partner is beneficial (see above).

Definitions:

Levels of Evidence

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

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- Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate diagnosis, treatment, and management of non-gonococcal urethritis
- Reduced number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI or undergoing investigations for possible infection

POTENTIAL HARMS

In persistent/recurrent cases, *Moxifloxacin* is no longer recommended as a 1st line therapy due to recent safety concerns (an increased risk of life threatening liver reactions and other serious risks) from the UK Medicines and Healthcare Products Regulatory Agency. It is now placed as a 2nd line therapy.

QUALIFYING STATEMENTS

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The recommendation of this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Clinical Effectiveness Group. 2007 UK national guideline on the management of non-gonococcal urethritis. London (UK): British Association for Sexual Health and HIV (BASHH); 2008 Dec. 26 p. [84 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2008 Dec)

GUIDELINE DEVELOPER(S)

British Association for Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

No specific or external funding was sought or provided in the development of this guideline.

GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Dr Mohsen Shahmanesh

Clinical Effectiveness Group (CEG) Members: Keith Radcliffe (*Chairman*); Imtyaz Ahmed-Jushuf; David Daniels; Mark FitzGerald; Neil Lazaro; Gillian McCarthy; Guy Rooney

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Conflicts of interest: None

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available from the British Association of Sexual Health and HIV Web Site.

AVAILABILITY OF COMPANION DOCUMENTS

Auditable outcome measures are provided in the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 15, 2000. The information was verified by the guideline developer on October 13, 2000. This summary was updated by ECRI on June 24, 2002 and March 9, 2009. The information was verified by the guideline developer in March 2009.

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